PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 September 2000 (01.09.00)	
International application No. PCT/GB00/00503	**Applicant's or agent's file reference** P/23582.WO/ICB
International filing date (day/month/year) 15 February 2000 (15.02.00)	**Priority date** (day/month/year) 16 February 1999 (16.02.99)
Applicant DAVIS, Peter, David	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

03 August 2000 (03.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Zakaria EL KHODARY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Articl 18 and Rul s 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
P/23582.WO/ICB		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 00503	15/02/2000	16/02/1999
Applicant		
ANGIOGENE PHARMACEUTICALS LTD. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/00503

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17 and 18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/00503

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61P35/00 A61P17/00 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 641 767 A (AJINOMOTO KK) 8 March 1995 (1995-03-08) abstract page 2, line 1 - line 40 examples tables 1,2 claims 1-10 ---	1-18
X	WO 92 16486 A (ASTON MOLECULES LTD) 1 October 1992 (1992-10-01) abstract page 1, line 26 -page 3, line 25 page 3, line 27 - line 36 claims 1-18 --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 2000	25. 05. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Taylor, G.M.

2

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/GB 00/00503

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOJI OHSUMI ET AL: "Novel Combretastatin Analogues Effective against Murine Solid Tumors: Design and Structure-Activity Relationships" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 41, no. 16, 30 July 1998 (1998-07-30), pages 3022-3032-3032, XP002102895 ISSN: 0022-2623 tables 1,2,4-6 Conclusion ---	1-18
X	OHSUMI K ET AL: "Syntheses and antitumor activity of cis-restricted combretastatins: 5-membered heterocyclic analogues" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 22, 17 November 1998 (1998-11-17), pages 3153-3158, XP004143718 ISSN: 0960-894X Introduction Compounds 4 and 5 ---	1-18
X	GEORGE R PETTIT ET AL: "Antineoplastic Agents 322. Synthesis of Combretastin A-4 Produgs" ANTI-CANCER DRUG DESIGN,GB,BASINGSTOKE, vol. 10, no. 4, June 1995 (1995-06), pages 299-309-309, XP002102893 ISSN: 0266-9536 Summary Introduction Compounds 1e-1j, 2 page 306 -page 308 -----	1-18

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/00503

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0641767 A	08-03-1995	AT 174899 T	15-01-1999
		CA 2131683 A	09-03-1995
		CN 1105967 A,B	02-08-1995
		DE 69415445 D	04-02-1999
		DE 69415445 T	22-07-1999
		ES 2126068 T	16-03-1999
		GR 3029603 T	30-06-1999
		JP 7228558 A	29-08-1995
		SI 641767 T	30-04-1999
		US 5525632 A	11-06-1996
		US 5731353 A	24-03-1998
WO 9216486 A	01-10-1992	AU 1371992 A	21-10-1992

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

LADAS & PARRY
52-54 High Holborn
London WC1V 6RR
GRANDE BRETAGNE

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	09.11.2000
Applicant's or agent's file reference: P/23582.WO/ICB	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/00503	15/02/2000	16/02/1999

International Patent Classification (IPC) or both national classification and IPC

A61K31/195

Applicant

ANGIOGENE PHARMACEUTICALS LTD. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 16/06/2001.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Taylor, G.M.

Formalities officer (incl. extension of time limits)
Exner, K
Telephone No. +49 89 2399 7826

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".)*:

Description, pages:

1-18 as originally filed

Claims, No.:

1-18 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 17,18;

because:

☒ the said international application, or the said claims Nos. 17,18 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separat sh t

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-18
Inventive step (IS)	Claims	1-18
Industrial applicability (IA)	Claims	17,18

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section III

1. Claims 17 and 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V

2. Claims 1-5, 11 and 15-18 do not meet the requirements of Art. 33(2) PCT.

2.1 The definition of B in claims 1-5, ..., i.e. "a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems" is extremely broad. The further definition of this in the description on p.4, lines 14-25 is also broad and non-exhaustive. Thus, B could be absolutely *any* constituent part of an NOS inhibitor, such as the atoms C, H, N or O (as derived from N-nitroarginine).

As a consequence, the documents cited in the search report are considered to be novelty destroying in view of the cited passages.

3. Claim 1, if limited to a conjugate A-X-B as defined in claim 1, wherein group B is as defined in claims 6 (excluding "a group derived from ... nitric oxide synthase", which also falls within the objections outlined in Item 1 above) and 7-10, would appear to be both novel and inventive in view of the cited prior art, since no document discloses or suggests such molecules or their use as vascular damaging agents or their use in the treatment of diseases involving neovascularisation.

4. For the assessment of the present claims 17 and 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VIII

5. Claims 1, 2 and 15-18 do not meet the requirements of Art. 5 and 6 PCT because the expression "and prodrugs thereof" is extremely broad and not adequately supported by examples. It also attempts to define the claimed compounds by reference to a result to be achieved, viz. a compound which is converted into the active compound *in vivo*. As a consequence, the subject-matter of the claim is not defined clearly in terms of technical features, as required by Rule 6.3(a) PCT.

6. Claim 12 is unclear (Art. 6 PCT) because the term "as hereinbefore described" is vague and, in part, makes reference to the description.

LANGNER PARRY

European Patent Attorneys
Chartered Patent Attorneys
Trade Mark Attorneys

09/890990

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9th February, 2001

VIA FACSIMILE: 00 49 89 2399-4465

International Preliminary Examining Authority,
The European Patent Office,
D-80298 Munich,
GERMANY.

Dear Sir,

Re: Angiogene Pharmaceuticals Ltd. et al
PCT Application PCT/GB00/00503
Our Ref: P/23582.WO/ICB

In reply to the Written Opinion dated 9th November, 2000.

We request the pages of claims (claims 1-18) be replaced by the attached pages of claims (claims 1-18) 3 copies of these claims will accompany the confirmation of this fax.

In claims 1, 2, 15, 16, 17 and 18 the group B has been characterised by a moiety which has inhibitor properties and joined to the rest of the molecule by a valency bond. We submit that the requirement of inhibitor properties is implicit in the description as in the function by a valency bond as distinct from a ionic structure.

In respect of Section III and Section V(4) claims 17 and 18 are acceptable in certain jurisdictions and are therefore relevant for assertion in these countries in the national phase.

In respect of Section V we submit that the application as filed makes it clear that the moiety must have inhibitor properties and the use of the term moiety is to emphasise derivation in the group from a compound of molecular structure

Continued.../

which is an independent compound with this inhibitor property. We submit that the amendment makes it clear that this moiety could not be a single atom derived from such a compound. The references cited do not disclose compounds in which part of the structure has such inhibitor function. As pointed out by the Examiner claim 6 which specifies groups having these inhibitor properties are undeniably novel.

In respect of Section VIII we submit that a "pro-drug" is well understood as defining compounds which are so functionally close to the compounds specified in the claims as to be functionally equivalent thereof. A simple list will determine whether a "pro-drug" is in fact of appropriate structure for the purpose of conversion from a structure to that of the claim. There is no inherent objection to defining choice of a structure to one complying with a single non-inventive test.

We submit the amended claims are acceptable for issuance of a favourable opinion.

Please acknowledge receipt of this letter and enclosures by return of the attached postal card.

Yours faithfully,

MARTYN W. MOLYNEAUX

Enc.
MWM/LH

CLAIMS:

1. A vascular damaging agent which is a compound of formula IA

A-X-B

IA

Wherein

A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems said moiety having said inhibiter properties and attached to the molecule by a valency bond

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

2. A vascular damaging agent which is a compound of formula I

A-X-B

I

Wherein

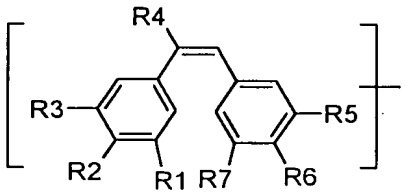
A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of nitric oxide synthase said moiety having inhibitor properties and attached to the molecule by a valency bond

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

3. A vascular damaging agent according to claim 2 in which the *cis*-stilbene moiety is a group of formula II



II

Wherein

R1, R2 and R3 are each independently H, optionally substituted alkoxy, optionally substituted alkyl or halogen

R4 is hydrogen or cyano

R5, R6 and R7 are each independently H, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, halogen, amino, alkylamino, dialkylamino, cyano, nitro, carboxyl, alkanoyl, alkoxycarbonyl, alkoxycarbonyloxy, alkoxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylcarbonylamino, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, dialkylaminosulphonyl, alkylsulphonylamino, aminosulphonylamino, alkylaminosulphonylamino, dialkylaminosulphonylamino, mercapto, alkylsulphanyl or alkylsulphinyl,

with the proviso that at least two of R1, R2 and R3 must be optionally substituted alkoxy.

4. An agent according to either of claims 2 and 3 in which the linker group X is a bond.

5. An agent according to either of claims 2 and 3 in which the linker group is selected from an optionally substituted methylene chain, or -$(CH_2)_m$-Y-$(CH_2)_n$- wherein Y is selected from -O-, -S-, -S(O)-, -SO_2-,-NH-, -Nalkyl-, -CO-, -OC(O)-, -NHC(O)-, -N(alkyl)C(O)-, -NHC(O)NH-, -NalkylC(O)NH-, -NalkylC(O)Nalkyl-, -$NHSO_2$-, -NalkylSO_2-, -$NHSO_2NH$-, -NalkylSO_2NH-, -NalkylSO_2Nalkyl- and -OC(O)O-, m is 0-3 and n is 0-3.

6. An agent according to any one of claims 2 to 5 in which the nitric oxide synthase inhibitor moiety is selected from a group derived from an amino acid inhibitor of nitric oxide synthase. a thiocitrulline derivative, an S-alkylisothiourea derivative or 2-aminopyridine derivative.

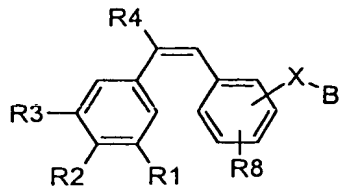
7. An agent according to claim 6 in which the group derived from an amino acid inhibitor of nitric oxide synthase is a group -C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio, or a group -NHCH(CO_2R10)-(CH_2)p-NHC(NH)Z where p and Z are as hereinbefore described and R10 is hydrogen or alkyl.

8. An agent according to claim 6 in which the thiocitrulline group is -C(O)CH(NH_2)-(CH_2)p-NHC(S)NH_2 or a group -NHCH(CO_2R10)-(CH_2)p-NHC(S)NH_2 .

9. An agent according to claim 6 in which the derivative of S-alkylisothiourea is -(CH_2)p-SC(NH)NH_2 .

10. An agent according to claim 6 in which the derivative of 2-aminopyridine is 4-methyl-2-pyridinylamino.

11. An agent according to claim 2 wherein the compound is



III

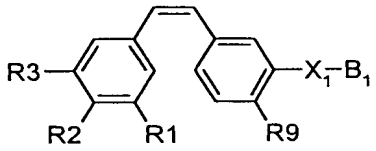
Wherein

R1, R2, R3, R4, X and B are as hereinbefore described

R8 is alkyl, amino, hydroxy, alkoxy or halogen

12. An agent according to claim 11 wherein the compounds are of formula III wherein R1, R2, R3, R4, are as hereinbefore described, R8 is alkyl, amino, hydroxy, alkoxy or halogen, X is -O- or -NH- and B is a group -C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio or a group -NHCH(CO_2R10)-(CH_2)p-NHC(NH)Z where p, Z and R10 are as hereinbefore described.

13. An agent according to claim 1 wherein the agent is of formula



IV

Wherein

R1, R2 and R3 are as hereinbefore described

R9 is alkyl, alkoxy or halogen

X_1 is O or NH

B_1 is a group -C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio.

14. An agent according to claim 2 which is selected from

(*Z*)-1-(4-Methoxy-3-N^G-nitroarginyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene
(*Z*)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine methyl ester
(*Z*)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine
(*Z*)-N-[2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine methyl ester

15. Use of a substituted stilbene compound in preparation of a medicament for the treatment of diseases involving neovascularisation characterised in that the stilbene compound is of formula IA

A-X-B

IA

Wherein

A is a substituted *cis*-stilbene moiety
X is a linker bond, atom or group
B is a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems said moiety having inhibitor properties and attached to the molecule by a valency bond

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

16. Use of a substituted stilbene compound in preparation of a medicament for the treatment of diseases involving neovascularisation characterised in that the stilbene compound is of formula I

A-X-B

I

Wherein

A is a substituted *cis*-stilbene moiety
X is a linker bond, atom or group
B is a moiety derived from an inhibitor of nitric oxide synthase said moiety having inhibitor properties and attached to the molecule by a valency bond

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

17. A method for the treatment of diseases involving neovascularisation characterised by the administration of a stilbene derivative of formula I

A-X-B

IA

Wherein

A is a substituted *cis*-stilbene moiety
X is a linker bond, atom or group
B is a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems said moiety having inhibitor properties and attached to the molecule by a valency bond

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

18. A method for the treatment of diseases involving neovascularisation characterised by the administration of a stilbene derivative of formula I

A-X-B

I

Wherein

A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of nitric oxide synthase said moiety having inhibitor properties and attached to the molecule by a valency bond

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P/23582.WO/ICB		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/00503	15/02/2000	16/02/1999
International Patent Classification (IPC) or national classification and IPC A61K31/195		
Applicant ANGIOGENE PHARMACEUTICALS LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/08/2000	07.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Taylor, G.M. Telephone No. +49 89 2399 8406

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00503

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-18	as originally filed				

Claims, No.:

1-18	as received on	09/02/2001	with letter of	09/02/2001	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☒ the entire international application.

   ☐ claims Nos. .

because:

   ☒ the said international application, or the said claims Nos. 17,18 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☒ the claims, or said claims Nos. 1,2,15-18 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-16

No: Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Section III

1. The amendments filed with the letter dated 09.02.2001 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. Thus, the addition of the expression

"said moiety having said inhibiter [*sic.*] properties and attached to the molecule by a valence bond"

finds no support in the application as filed. Moreover, this wording cannot be seen as being implicit from the description.

1.1 The expression "valency bond" is further more unclear (Art. 6 PCT) in what it is intended to characterise. The term "valency" is used to refer to the number of bonds formed by an atom

It may be that this expression was intended to refer to a *covalent* bond, as distinct from an ionic bond. However, there is apparently no support in the description for such a selection; likewise, there are no clear expressions such as *covalent bond.*

1.2 As a consequence of the above, the following IPER is based upon claims 1-18 **as originally filed.**

2. Claims 17 and 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V

3. Claims 1-5, 11 and 15-18 do not meet the requirements of Art. 33(2) PCT.

3.1 The definition of B in claims 1-5, ..., i.e. "a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems" is extremely broad. The further definition of this in the description on p.4, lines 14-25 is also broad and non-exhaustive. Thus, B could be absolutely any constituent part of an NOS inhibitor, such as the atoms C, H, N or O (as derived from N-nitroarginine).

As a consequence, the documents cited in the search report are considered to be novelty destroying in view of the cited passages.

4. Claim 1, if limited to a conjugate A-X-B as defined in claim 1, wherein group B is as defined in claims 6 (excluding "a group derived from ... nitric oxide synthase", which also falls within the objections outlined in Item 1 above) and 7-10, would appear to be both novel and inventive in view of the cited prior art, since no document discloses or suggests such molecules or their use as vascular damaging agents or their use in the treatment of diseases involving neovascularisation.

5. For the assessment of the present claims 17 and 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VIII

6. Claims 1, 2 and 15-18 do not meet the requirements of Art. 5 and 6 PCT because the expression "and prodrugs thereof" is extremely broad and not adequately supported by examples. It also attempts to define the claimed compounds by reference to a result to be achieved, viz. a compound which is converted into the active compound *in vivo*.

   Thus, an ester of one active compound, e.g. an acetate, might not act as a pro-drug for another; *in vivo* release of drugs is extremely compound-specific and cannot be reliably predicted.

   As a consequence, the subject-matter of the claim is not defined clearly in terms of technical features, as required by Rule 6.3(a) PCT.

7. Claim 12 is unclear (Art. 6 PCT) because the term "as hereinbefore described" is vague and, in part, makes reference to the description.

CLAIMS:

1. A vascular damaging agent which is a compound of formula IA

A-X-B

IA

Wherein

A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

2. A vascular damaging agent which is a compound of formula I

A-X-B

I

Wherein

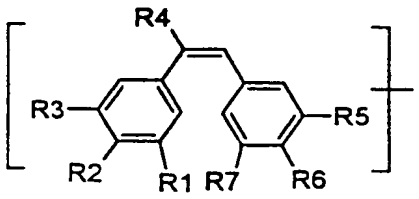
A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of nitric oxide synthase

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

3. A vascular damaging agent according to claim 2 in which the *cis*-stilbene moiety is a group of formula II



II

Wherein

R1, R2 and R3 are each independently H, optionally substituted alkoxy, optionally substituted alkyl or halogen

R4 is hydrogen or cyano

R5, R6 and R7 are each independently H, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, halogen, amino, alkylamino, dialkylamino, cyano, nitro, carboxyl, alkanoyl, alkoxycarbonyl, alkoxycarbonyloxy, alkoxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylcarbonylamino, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, dialkylaminosulphonyl, alkylsulphonylamino, aminosulphonylamino, alkylaminosulphonylamino, dialkylaminosulphonylamino, mercapto, alkylsulphanyl or alkylsulphinyl,

with the proviso that at least two of R1, R2 and R3 must be optionally substituted alkoxy.

4. An agent according to either of claims 2 and 3 in which the linker group X is a bond.

5. An agent according to either of claims 2 and 3 in which the linker group is selected from an optionally substituted methylene chain, or $-(CH_2)_m-Y-(CH_2)_n-$ wherein Y is selected from -O-, -S-, -S(O)-, $-SO_2-$,-NH-, -Nalkyl-, -CO-, -OC(O)-, -

NHC(O)-, -N(alkyl)C(O)-, -NHC(O)NH-, -NalkylC(O)NH-, -NalkylC(O)Nalkyl-, -$NHSO_2$-, -NalkylSO_2-, -$NHSO_2NH$-, -NalkylSO_2NH-, -NalkylSO_2Nalkyl- and -OC(O)O-, m is 0-3 and n is 0-3.

6. An agent according to any one of claims 2 to 5 in which the nitric oxide synthase inhibitor moiety is selected from a group derived from an amino acid inhibitor of nitric oxide synthase. a thiocitrulline derivative, an S-alkylisothiourea derivative or 2-aminopyridine derivative.

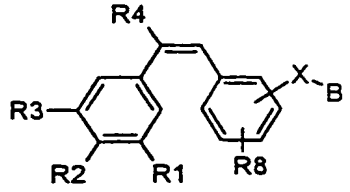
7. An agent according to claim 6 in which the group derived from an amino acid inhibitor of nitric oxide synthase is a group -C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio, or a group -NHCH(CO_2R10)-(CH_2)p-NHC(NH)Z where p and Z are as hereinbefore described and R10 is hydrogen or alkyl.

8. An agent according to claim 6 in which the thiocitrulline group is -C(O)CH(NH_2)-(CH_2)p-NHC(S)NH_2 or a group -NHCH(CO_2R10)-(CH_2)p-NHC(S)NH_2 .

9. An agent according to claim 6 in which the derivative of S-alkylisothiourea is -(CH_2)p-SC(NH)NH_2 .

10. An agent according to claim 6 in which the derivative of 2-aminopyridine is 4-methyl-2-pyridinylamino.

11. An agent according to claim 2 wherein the compound is



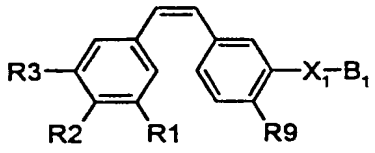
III

Wherein

R1, R2, R3, R4, X and B are as hereinbefore described
R8 is alkyl, amino, hydroxy, alkoxy or halogen

12. An agent according to claim 11 wherein the compounds are of formula III wherein R1, R2, R3, R4, are as hereinbefore described, R8 is alkyl, amino, hydroxy, alkoxy or halogen, X is -O- or -NH- and B is a group -C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio or a group -NHCH(CO_2R10)-(CH_2)p-NHC(NH)Z where p, Z and R10 are as hereinbefore described.

13. An agent according to claim 1 wherein the agent is of formula



IV

Wherein
R1, R2 and R3 are as hereinbefore described
R9 is alkyl, alkoxy or halogen
X_1 is O or NH
B_1 is a group -C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio.

14. An agent according to claim 2 which is selected from
(Z)-1-(4-Methoxy-3-N^G-nitroarginyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene
(Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine methyl ester
(Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine

(*Z*)-N-[2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine methyl ester

15. Use of a substituted stilbene compound in preparation of a medicament for the treatment of diseases involving neovascularisation characterised in that the stilbene compound is of formula IA

A-X-B

IA

Wherein

A is a substituted *cis*-stilbene moiety
X is a linker bond, atom or group
B is a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

16. Use of a substituted stilbene compound in preparation of a medicament for the treatment of diseases involving neovascularisation characterised in that the stilbene compound is of formula I

A-X-B

I

Wherein

A is a substituted *cis*-stilbene moiety
X is a linker bond, atom or group

B is a moiety derived from an inhibitor of nitric oxide synthase

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

17. A method for the treatment of diseases involving neovascularisation characterised by the administration of a stilbene derivative of formula I

A-X-B

IA

Wherein

A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

18. A method for the treatment of diseases involving neovascularisation characterised by the administration of a stilbene derivative of formula I

A-X-B

I

Wherein

A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of nitric oxide synthase

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

A4

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P/23582.WO/ICB		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/00503	15/02/2000	16/02/1999
International Patent Classification (IPC) or national classification and IPC A61K31/195		
Applicant ANGIOGENE PHARMACEUTICALS LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/08/2000	07.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Taylor, G.M. Telephone No. +49 89 2399 8406

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00503

I. Basis of the r p rt

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-18	as originally filed				

Claims, No.:

1-18	as received on	09/02/2001	with letter of	09/02/2001	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☒ the entire international application.

   ☐ claims Nos. .

because:

   ☒ the said international application, or the said claims Nos. 17,18 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☒ the claims, or said claims Nos. 1,2,15-18 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-16

No: Claims

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

S ction III

1. The amendments filed with the letter dated 09.02.2001 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. Thus, the addition of the expression

   "said moiety having said inhibiter [*sic.*] properties and attached to the molecule by a valence bond"

   finds no support in the application as filed. Moreover, this wording cannot be seen as being implicit from the description.

1.1 The expression "valency bond" is further more unclear (Art. 6 PCT) in what it is intended to characterise. The term "valency" is used to refer to the number of bonds formed by an atom

It may be that this expression was intended to refer to a *covalent* bond, as distinct from an ionic bond. However, there is apparently no support in the description for such a selection; likewise, there are no clear expressions such as *covalent bond.*

1.2 As a consequence of the above, the following IPER is based upon claims 1-18 **as originally filed**.

2. Claims 17 and 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V

3. Claims 1-5, 11 and 15-18 do not meet the requirements of Art. 33(2) PCT.

3.1 The definition of B in claims 1-5, ..., i.e. "a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems" is extremely broad. The further definition of this in the description on p.4, lines 14-25 is also broad and non-exhaustive. Thus, B could be absolutely any constituent part of an NOS inhibitor, such as the atoms C, H, N or O (as derived from N-nitroarginine).

As a consequence, the documents cited in the search report are considered to be novelty destroying in view of the cited passages.

4. Claim 1, if limited to a conjugate A-X-B as defined in claim 1, wherein group B is as defined in claims 6 (excluding "a group derived from ... nitric oxide synthase", which also falls within the objections outlined in Item 1 above) and 7-10, would appear to be both novel and inventive in view of the cited prior art, since no document discloses or suggests such molecules or their use as vascular damaging agents or their use in the treatment of diseases involving neovascularisation.

5. For the assessment of the present claims 17 and 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VIII

6. Claims 1, 2 and 15-18 do not meet the requirements of Art. 5 and 6 PCT because the expression "and prodrugs thereof" is extremely broad and not adequately supported by examples. It also attempts to define the claimed compounds by reference to a result to be achieved, viz. a compound which is converted into the active compound *in vivo*.

   Thus, an ester of one active compound, e.g. an acetate, might not act as a pro-drug for another; *in vivo* release of drugs is extremely compound-specific and cannot be reliably predicted.

   As a consequence, the subject-matter of the claim is not defined clearly in terms of technical features, as required by Rule 6.3(a) PCT.

7. Claim 12 is unclear (Art. 6 PCT) because the term "as hereinbefore described" is vague and, in part, makes reference to the description.

CLAIMS:

1. A vascular damaging agent which is a compound of formula IA

A-X-B

IA

Wherein

A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems said moiety having said inhibiter properties and attached to the molecule by a valency bond

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

2. A vascular damaging agent which is a compound of formula I

A-X-B

I

Wherein

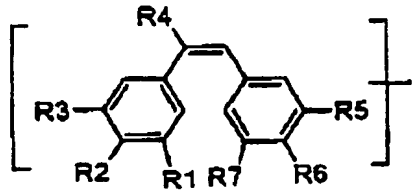
A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of nitric oxide synthase said moiety having inhibitor properties and attached to the molecule by a valency bond

and the hydrates. pharmaceutically acceptable salts and prodrugs thereof.

3. A vascular damaging agent according to claim 2 in which the *cis*-stilbene moiety is a group of formula II



II

Wherein

R1, R2 and R3 are each independently H, optionally substituted alkoxy, optionally substituted alkyl or halogen

R4 is hydrogen or cyano

R5, R6 and R7 are each independently H, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, halogen, amino, alkylamino, dialkylamino, cyano, nitro, carboxyl, alkanoyl, alkoxycarbonyl, alkoxycarbonyloxy, alkoxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylcarbonylamino, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, dialkylaminosulphonyl, alkylsulphonylamino, aminosulphonylamino, alkylaminosulphonylamino, dialkylaminosulphonylamino, mercapto, alkylsulphanyl or alkylsulphinyl,

with the proviso that at least two of R1, R2 and R3 must be optionally substituted alkoxy.

4. An agent according to either of claims 2 and 3 in which the linker group X is a bond.

5. An agent according to either of claims 2 and 3 in which the linker group is selected from an optionally substituted methylene chain, or -$(CH_2)_m$-Y-$(CH_2)_n$- wherein Y is selected from -O-, -S-, -S(O)-, -SO_2-,-NH-, -Nalkyl-, -CO-, -OC(O)-, -NHC(O)-, -N(alkyl)C(O)-, -NHC(O)NH-, -NalkylC(O)NH-, -NalkylC(O)Nalkyl-, -$NHSO_2$-, -NalkylSO_2-, -$NHSO_2NH$-, -NalkylSO_2NH-, -NalkylSO_2Nalkyl- and -OC(O)O-, m is 0-3 and n is 0-3.

6. An agent according to any one of claims 2 to 5 in which the nitric oxide synthase inhibitor moiety is selected from a group derived from an amino acid inhibitor of nitric oxide synthase. a thiocitrulline derivative, an S-alkylisothiourea derivative or 2-aminopyridine derivative.

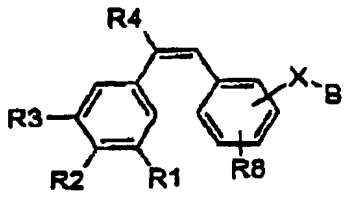
7. An agent according to claim 6 in which the group derived from an amino acid inhibitor of nitric oxide synthase is a group -C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio, or a group -NHCH(CO_2R10)-(CH_2)p-NHC(NH)Z where p and Z are as hereinbefore described and R10 is hydrogen or alkyl.

8. An agent according to claim 6 in which the thiocitrulline group is -C(O)CH(NH_2)-(CH_2)p-NHC(S)NH_2 or a group -NHCH(CO_2R10)-(CH_2)p-NHC(S)NH_2 .

9. An agent according to claim 6 in which the derivative of S-alkylisothiourea is -(CH_2)p-SC(NH)NH_2 .

10. An agent according to claim 6 in which the derivative of 2-aminopyridine is 4-methyl-2-pyridinylamino.

11. An agent according to claim 2 wherein the compound is



III

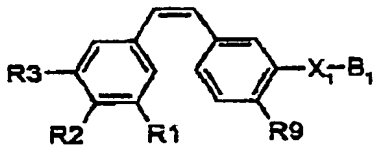
Wherein

R1, R2, R3, R4, X and B are as hereinbefore described

R8 is alkyl, amino, hydroxy, alkoxy or halogen

12. An agent according to claim 11 wherein the compounds are of formula III wherein R1, R2, R3, R4, are as hereinbefore described, R8 is alkyl, amino, hydroxy, alkoxy or halogen, X is -O- or -NH- and B is a group -C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio or a group -NHCH(CO_2R10)-(CH_2)p-NHC(NH)Z where p, Z and R10 are as hereinbefore described.

13. An agent according to claim 1 wherein the agent is of formula



IV

Wherein

R1, R2 and R3 are as hereinbefore described

R9 is alkyl, alkoxy or halogen

X_1 is O or NH

B_1 is a group -C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio.

14. An agent according to claim 2 which is selected from

(*Z*)-1-(4-Methoxy-3-N^G-nitroarginyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

(*Z*)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine methyl ester

(*Z*)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine

(*Z*)-N-[2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine methyl ester

15. Use of a substituted stilbene compound in preparation of a medicament for the treatment of diseases involving neovascularisation characterised in that the stilbene compound is of formula IA

A-X-B

IA

Wherein

A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems said moiety having inhibitor properties and attached to the molecule by a valency bond

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

16. Use of a substituted stilbene compound in preparation of a medicament for the treatment of diseases involving neovascularisation characterised in that the stilbene compound is of formula I

A-X-B

I

Wherein

A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of nitric oxide synthase said moiety having inhibitor properties and attached to the molecule by a valency bond

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

17. A method for the treatment of diseases involving neovascularisation characterised by the administration of a stilbene derivative of formula I

A-X-B

IA

Wherein

A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems said moiety having inhibitor properties and attached to the molecule by a valency bond

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

18. A method for the treatment of diseases involving neovascularisation characterised by the administration of a stilbene derivative of formula I

A-X-B

I

Wherein

A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of nitric oxide synthase said moiety having inhibitor properties and attached to the molecule by a valency bond

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

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(71) Applicant *(for all designated States except US)*: ANGIOGENE PHARMACEUTICALS LTD. [GB/GB]; 14 Plowden Park, Aston Rowant, Watlington, Oxfordshire OX9 5SW (GB).

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(54) Title: SUBSTITUTED STILBENE COMPOUNDS WITH VASCULAR DAMAGING ACTIVITY

(57) Abstract

Vascular damaging agents for use in treating diseases involving angiogenesis are provided which are compounds of formula: A–X–B, wherein A is a substituted cis–stilbene moiety, X a linker bond, atom or group and B is a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems specifically an inhibitor of nitric oxide synthase, and hydrates, pharmaceutically acceptable salts and prodrugs thereof. There are also provided compositions containing such compounds.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/00503

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61P35/00 A61P17/00 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 641 767 A (AJINOMOTO KK) 8 March 1995 (1995-03-08) abstract page 2, line 1 - line 40 examples tables 1,2 claims 1-10	1-18
X	WO 92 16486 A (ASTON MOLECULES LTD) 1 October 1992 (1992-10-01) abstract page 1, line 26 -page 3, line 25 page 3, line 27 - line 36 claims 1-18	1-18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
12 May 2000	25. 05. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Taylor, G.M.

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOJI OHSUMI ET AL: "Novel Combretastatin Analogues Effective against Murine Solid Tumors: Design and Structure-Activity Relationships" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 41, no. 16, 30 July 1998 (1998-07-30), pages 3022-3032-3032, XP002102895 ISSN: 0022-2623 tables 1,2,4-6 Conclusion	1-18
X	OHSUMI K ET AL: "Syntheses and antitumor activity of cis-restricted combretastatins: 5-membered heterocyclic analogues" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 22, 17 November 1998 (1998-11-17), pages 3153-3158, XP004143718 ISSN: 0960-894X Introduction Compounds 4 and 5	1-18
X	GEORGE R PETTIT ET AL: "Antineoplastic Agents 322. Synthesis of Combretastin A-4 Produgs" ANTI-CANCER DRUG DESIGN,GB,BASINGSTOKE, vol. 10, no. 4, June 1995 (1995-06), pages 299-309-309, XP002102893 ISSN: 0266-9536 Summary Introduction Compounds 1e-1j, 2 page 306 -page 308	1-18

2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/00503

Box I Obs rvation where certain laims were found unsearchable (Continuati n of it m 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17 and 18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/00503

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0641767 A	08-03-1995	AT 174899 T	15-01-1999
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		DE 69415445 D	04-02-1999
		DE 69415445 T	22-07-1999
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		JP 7228558 A	29-08-1995
		SI 641767 T	30-04-1999
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WO 9216486 A	01-10-1992	AU 1371992 A	21-10-1992

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SUBSTITUTED STILBENE COMPOUNDS WITH VASCULAR DAMAGING ACTIVITY

This invention relates to vascular damaging agents and particularly to a series of novel stilbene compounds.

Formation of new vasculature by angiogenesis is a key pathological feature of several diseases (J Folkman, New England Journal of Medicine 333, 1757-1763, 1995). For example, for a solid tumour to grow it must develop its own blood supply upon which it depends critically for the provision of oxygen and nutrients; if this blood supply is mechanically shut off the tumour undergoes necrotic death. Neovascularisation is also a clinical feature of skin lesions in psoriasis, of the invasive pannus in the joints of rheumatoid arthritis patients and of atherosclerotic plaques. Retinal neovascularisation is pathological in macular degeneration and in diabetic retinopathy. In all these diseases reversal of neovascularisation by damaging the newly-formed vascular endothelium is expected to have a beneficial therapeutic effect.

Combretastatin A4 phosphate is an agent known to have vascular damaging activity in animal models of solid tumours (Dark et al, Cancer Research 57, 1829-1834, 1997). However some tumours are resistant to this agent and doses approaching the maximum tolerated dose are necessary to produce significant vascular damage in these tumours.

One characteristic of tumours resistant to combretastatin A4 phosphate is their ability to produce large amounts of nitric oxide. The role of nitric oxide in tumour growth is unclear and there have been reports of both tumour-stimulating and tumour-inhibiting effects (Chinje and Stratford, Essays Biochem. 32, 61-72, 1997).

The present invention concerns novel combretastatin derivatives, methods for their preparation, pharmaceutical compositions containing them and their use as vascular damaging agents for the treatment of diseases involving active angiogenesis. These derivatives are more active than combretastatin A4 phosphate, particularly on tumours

that are resistant to the known vascular damaging agents. In solid tumours vascular damaging agents exert their anti-tumour effect largely by inducing necrosis in the tumour, through starvation of the tumour's blood supply. Compounds of the invention show improved activity in the induction of necrosis in solid tumours. Though not limiting on the invention it is believed that the ability of compounds of the invention to reduce the production of nitric oxide during vascular damage by inhibition of one or more of the enzymes that produce nitric oxide (the nitric oxide synthases), is one way in which the compounds achieve increased activity.

Thus in one embodiment of the invention there is provided a compound of formula IA

A-X-B

IA

Wherein

A is a substituted *cis*-stilbene moiety
X is a linker bond, atom or group
B is a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

In a more specific embodiment of the invention there is provided a vascular damaging agent which is a compound of formula I

A-X-B

I

Wherein

A is a substituted *cis*-stilbene moiety

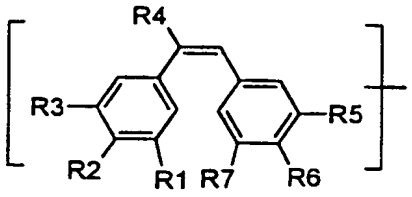
X is a linker bond, atom or group

B is a moiety derived from an inhibitor of nitric oxide synthase

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

The linker X can be attached to any available atom of the stilbene moiety A and to any available atom of nitric oxide synthase inhibitor B as appropriate.

The stilbene moiety A can be for example a group of formula II



II

Wherein

R1, R2 and R3 are each independently H, optionally substituted alkoxy, optionally substituted alkyl or halogen

R4 is hydrogen or cyano

R5, R6 and R7 are each independently H, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, halogen, amino, alkylamino, dialkylamino, cyano, nitro, carboxyl, alkanoyl, alkoxycarbonyl, alkoxycarbonyloxy, alkoxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylcarbonylamino, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, dialkylaminosulphonyl, alkylsulphonylamino, aminosulphonylamino, alkylaminosulphonylamino, dialkylaminosulphonylamino, mercapto, alkylsulphanyl or alkylsulphinyl,

with the proviso that at least two of R1, R2 and R3 must be optionally substituted alkoxy.

Stilbene moiety A can be attached to linker group X by any available valency.

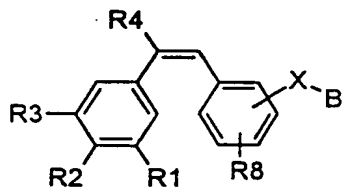
Linker group X can be for example a bond, an optionally substituted methylene chain, or $-(CH_2)_m-Y-(CH_2)_n-$ wherein Y is selected from -O-, -S-, -S(O)-, $-SO_2-$,-NH-, -Nalkyl-, -CO-, -OC(O)-, -NHC(O)-, -N(alkyl)C(O)-, -NHC(O)NH-, -NalkylC(O)NH-, -NalkylC(O)Nalkyl-, $-NHSO_2-$, $-NalkylSO_2-$, $-NHSO_2NH-$, $-NalkylSO_2NH-$, -$NalkylSO_2$Nalkyl- and -OC(O)O-, m is 0-3 and n is 0-3. Where the group Y is not symmetrical it can be oriented in either direction such that either end can be attached to the group A.

The nitric oxide synthase inhibitor moiety B can be a group derived from an inhibitor of nitric oxide synthase. Such inhibitors include, for example a group derived from an amino acid inhibitor of nitric oxide synthesis for example a group $-C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z$ wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio, or for example a group $-NHCH(CO_2R10)-(CH_2)p-NHC(NH)Z$ where p and Z are as hereinbefore described and R10 is hydrogen or alkyl. A further example of a nitric oxide synthase inhibitor moiety B is a group derived from thiocitrulline for example a group $-C(O)CH(NH_2)-(CH_2)p-NHC(S)NH_2$ or a group $-NHCH(CO_2R10)-(CH_2)p-NHC(S)NH_2$. A further example of a nitric oxide synthase inhibitor moiety B is a group derived from an S-alkylisothiourea for example $-(CH_2)p-SC(NH)NH_2$. A further example of a nitric oxide synthase inhibitor moiety B is a group derived from a 2-aminopyridine for example a 4-methyl-2-pyridinylamino group.

As used herein the term "alkyl", alone or in combinations, means a straight or branched-chain alkyl group containing from one to seven, preferably a maximum of four, carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl and pentyl. Examples of alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy and t-butoxy. The term "halogen" means fluorine, chlorine, bromine or iodine.

Optionally substituted alkoxy groups , optionally substituted alkyl groups and optionally substituted methylene chains may bear one or more substituents independently selected from halogen, hydroxy, amino, alkylamino, dialkylamino, carboxyl, mercapto, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, alkylcarbonyl(alkyl)amino, sulphate and phosphate.

One group of preferred compounds are those of formula III



III

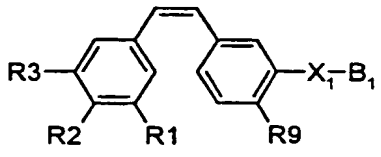
Wherein

R1, R2, R3, R4, X and B are as hereinbefore described

R8 is alkyl, amino, hydroxy, alkoxy or halogen

A further preferred group of compounds are those of formula III wherein R1, R2, R3, R4, are as hereinbefore described, R8 is alkyl, amino, hydroxy, alkoxy or halogen, X is -O- or -NH- and B is a group $-C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z$ wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio or a group $-NHCH(CO_2R10)-(CH_2)p-NHC(NH)Z$ where p, Z and R10 are as hereinbefore described.

A still further preferred subset includes compounds of formula IV



IV

Wherein

R1, R2 and R3 are as hereinbefore described

R9 is alkyl, alkoxy or halogen

X_1 is O or NH

B_1 is a group -C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio.

Particularly preferred compounds include:

(*Z*)-1-(4-Methoxy-3-N^G-nitroarginyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

(*Z*)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine methyl ester

(*Z*)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine

(*Z*)-N-[2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine methyl ester

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by "hereinbefore defined" or "defined hereinbefore", or "hereinafter defined" or "defined hereinafter", the said group encompasses the first occurring and broadest definition as well as each and all of the preferred definitions for that group.

Where one or more functional groups in compounds of formula I are sufficiently basic or acidic the formation of salts is possible. Suitable salts include pharmaceutically acceptable salts for example acid addition salts including hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates and tartrates, salts derived from inorganic bases including alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and salts derived from organic amines such as morpholine, piperidine or dimethylamine salts.

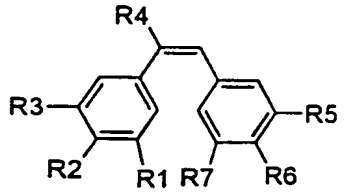
Compounds of formula I or IA or a salt thereof may exhibit tautomerism and the formulae drawings within this specification represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form that has vascular damaging activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings.

Those skilled in the art will recognise that compounds of formula I or IA may exist as stereoisomers and accordingly the present invention includes all such isomers and mixtures thereof which have vascular damaging activity. Where the group derived from a nitric oxide synthase inhibitor is derived from an amino acid inhibitor of nitric oxide synthase the L-configuration of the amino acid is preferred.

Compounds of the invention can be prepared by any process known to a person skilled in the art. Compounds of formulae IA, I, III and IV can be prepared by a number of processes as generally described hereinbelow and more specifically in the Examples hereinafter. In the general preparations described below it may be necessary to employ protecting groups which are then removed during the final stages of the synthesis. The appropriate use of such protecting groups and processes for their removal will be readily apparent to those skilled in the art. In the following process description, the symbols R1, R2, R3, R4, R5, R6, R7, X and B when used in the formulae depicted are to be understood to represent those groups described above in relation to formula I unless otherwise indicated

Thus according to a further aspect of the invention compounds of the invention may be prepared by attachment of a nitric oxide synthase inhibitor to a stilbene of formula V using alkylation, acylation, sulphonylation or coupling reactions. Alternatively stilbenes of formula V may be coupled to a difunctional compound (which provides the linker group -X-) and further coupled to the nitric oxide inhibitor via the remaining functionality on the linker group as appropriate. Stilbenes of formula V are either known or can be prepared using methods analagous to those used in the preparation of the known stilbenes which will be apparent to those skilled in the art.

In one general example compounds of formulae I can be prepared from a stilbene of formula V containing a free OH or NH by acylation with a nitric oxide synthase inhibitor containing a carboxylic acid for example using a coupling agent such as a carbodiimide, for example dicyclohexylcarbodiimide, or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and, optionally, a base such as an organic base for example triethylamine and, optionally, a catalyst such as 4-dimethyaminopyridine in a solvent such as an aprotic solvent for example dimethylformamide or in a chlorinated solvent for example chloroform or dichloromethane at a temperature in the range from about -30°C to about 60°C, conveniently at or near room temperature.



V

In another general example a compound or formula V containing a free OH or NH group can be treated with 4-nitrophenylchloroformate in a solvent such as pyridine at a temperature of about -10°C to room temperature followed by treatment with a nitric oxide synthase inhibitor containing a free OH or NH group to give a compound of formula 1 containing a carbonate, carbamate or urea group.

In another general example a compound of formula V containing a free NH group can be treated with a dicarboxylic acid monoester such as monomethyl succinate in the presence of a coupling agent such as a carbodiimide, for example dicyclohexylcarbodiimide, or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and, optionally, a base such as an organic base for example triethylamine in a solvent such as an aprotic solvent for example dimethylformamide or in a chlorinated solvent for example chloroform or dichloromethane at a temperature in the range from about -30°C to about 60°C, conveniently at or near room temperature. The resulting ester can be hydrolysed by treatment with aqueous acid or aqueous base under standard

conditions and the carboxylic acid so obtained treated with a nitric oxide inhibitor containing a free OH or NH group, using a coupling agent as described hereinbefore, to give compounds of the invention.

In another general example a compound of formula V containing a carboxylic acid group can be converted into a compound of formula I containing an amide or ester by treatment with a nitric oxide synthase inhibitor, containing an amino group or a hydroxyl group respectively, using a coupling agent as described hereinbefore.

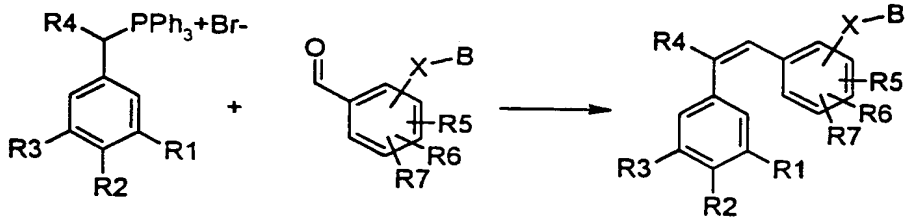
In another general example a compound of formula V containing a monohaloalkyl group can be reacted with a nitric oxide synthase inhibitor containing a free OH, NH, or SH group in the presence of a base such as sodium carbonate or a metal hydride such as sodium hydride in a solvent such as dimethylformamide at a temperature of about 0°C to a temperature of about 100°C to give compounds of the invention.

In another general example a compound of formula V containing a carboxylic acid group can be treated with a monoprotected diamino, dihydroxy or aminohydroxy compound such as a monoprotected diaminoalkane, a monoprotected dihydroxyalkane or mono-protected aminohydroxyalkane, using a coupling agent as described hereinbefore and the resulting amide or ester deprotected and reacted with a nitric oxide synthase inhibitor containing a carboxylic acid using a coupling agent as described hereinbefore.

In another general example a compound of formula V containing a free OH or NH group can be sulphonylated with a protected amino sulphonylchloride such as a protected aminoalkylsulphonylchloride or a protected hydroxy sulphonyl chloride such as a protected hydroxyalkylsulphonyl chloride, in the presence of a base, for example a tertiary amine base such as triethylamine, in for example a solvent such as a hydrocarbon solvent e.g. dichloromethane at a temperature in the range for example -30°C to 120°C, conveniently at or near ambient temperature and the resulting sulphonamide or sulphonate deprotected and reacted with a nitric oxide synthase inhibitor containing a carboxylic acid using a coupling agent as described hereinbefore.

In another general example a compound of formula V containing a free OH, SH or NH group can be alkylated with a difunctional alkylating agent such as a dihaloalkane in the presence of a base such as sodium carbonate or a metal hydride such as sodium hydride in a solvent such as dimethylformamide at a temperature of about 0°C to a temperature of about 100°C, and the resulting haloalkane further reacted under similar conditions with a nitric oxide synthase inhibitor containing a free OH, SH or NH group.

Compounds of formula VII can also be prepared by Wittig olefin synthesis involving reaction of a phosphonium salt of formula VI with a strong base, for example an alkyllithium such as n-butyllithium or t-butyllithium or a metal hydride such as sodium hydride in a solvent such as an ether solvent for example diethyl ether or tetrahydrofuran or in a solvent such as a hydrocarbon solvent for example toluene at a temperature of between about -100°C to about 30°C followed by treatment with an aldehyde of formula VII.



VI VII VIII

Compounds of formula I can also be prepared from other compounds of formula I by chemical modification. Examples of such chemical modifications that may be applied are standard alkylation, acylation, thioacylation, sulphonylation, aromatic halogenation and coupling reactions. These reactions may be used to add new substituents or to modify existing substituents. Alternatively, existing substituents in compounds of formula I may be modified by, for example, oxidation, reduction, elimination, hydrolysis or other cleavage reaction to yield other compounds of formula I.

Thus for example a compound of formula I containing an amino group may be acylated on the amino group by treatment with, for example, an acyl halide or anhydride in the presence of a base, for example a tertiary amine base such as triethylamine, in for example, a solvent such as a hydrocarbon solvent e.g. dichloromethane at a temperature in the range for example -30°C to 120°C, conveniently at or near ambient temperature.

In another general example of an interconversion process an amino group in a compound of formula I may be sulphonylated by treatment with, for example, an alkyl or aryl sulphonyl chloride or an alkyl or aryl sulphonic anhydride in the presence of a base, for example a tertiary amine base such as triethylamine, in for example a solvent such as a hydrocarbon solvent e.g. dichloromethane at a temperature in the range for example -30°C to 120°C, conveniently at or near ambient temperature.

In a further general example a compound of formula 1 containing an ester can be hydrolysed by treatment with an acid, for example sulphuric acid, in a solvent such as tetrahydrofuran in the presence of water at a temperature of about room temperature to the reflux temperature of the solvent, preferably at or around 60°C.

In a further general example a compound of formula I containing an amide can be hydrolysed by treatment with for example an acid such as hydrochloric acid in a solvent such as an alcohol, for example methanol at an elevated temperature conveniently at the reflux temperature.

In another general example an O-alkyl group may be cleaved to the corresponding alcohol (OH) by reaction with boron tribromide in a solvent such as a chlorinated solvent e.g. dichloromethane at a low temperature e.g. around -78°C.

In a further general example compounds of formula I may be alkylated by reaction with a suitable alkylating agent such as an alkyl halide, an alkyl toluenesulphonate, an alkyl methanesulphonate or an alkyl triflate. The alkylation reaction can be carried out in

the presence of a base for example an inorganic base such as a carbonate e.g. caesium or potassium carbonate, a hydride such as sodium hydride or an alkoxide such as potassium t-butoxide in a suitable solvent such as an aprotic solvent e.g. dimethylformamide or an ether solvent such as tetrahydrofuran at a temperature of around -10 to 80°C.

Preparation of a compound of formula I as a single enantiomer or, where appropriate, diastereomer may be effected by synthesis from an enantiomerically pure starting material or intermediate or by resolution of the final product in a conventional manner.

Acid addition salts of the compounds of formula I are prepared in a conventional manner by treating a solution or suspension of the free base I with about one equivalent of a pharmaceutically acceptable acid. Salts of compounds of formula I derived from inorganic or organic bases are prepared in a conventional manner by treating a solution or suspension of the free acid I with about one equivalent of a pharmaceutically acceptable organic or inorganic base. Alternatively both acid addition salts and salts derived from bases may be prepared by treatment of the parent compound with the appropriate ion-exchange resin in a standard fashion. Conventional concentration and recrystallisation techniques are employed in isolating the salts.

Compounds according to the invention are able to destroy tumour vasculature and vasculature that has been newly formed while leaving unaffected normal, mature vasculature. The ability of the compounds to act in this way may be determined by the tests described in the Examples hereinafter.

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of cancers involving solid tumours and in the prophylaxis and treatment of diseases where inappropriate angiogenesis occurs such as diabetic retinopathy, psoriasis, rheumatoid arthritis, atherosclerosis and macular degeneration.

The compounds of the invention may be administered as a sole therapy or in combination with other treatments. For the treatment of solid tumours compounds of

the invention may be administered in combination with radiotherapy or in combination with other anti-tumour substances for example those selected from mitotic inhibitors, for example vinblastine, paclitaxel and docetaxel; alkylating agents, for example cisplatin, carboplatin and cyclophosphamide; antimetabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea; intercalating agents for example adriamycin and bleomycin; enzymes, for example aspariginase; topoisomerase inhibitors for example etoposide, topotecan and irinotecan; thymidylate synthase inhibitors for example raltitrexed; biological response modifiers for example interferon; antibodies for example edrecolomab; and anti-hormones for example tamoxifen. Such combination treatment may involve simultaneous or sequential application of the individual components of the treatment.

For the prophylaxis and treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions selected with regard to the intended route of administration and standard pharmaceutical practice. Such pharmaceutical compositions may take a form suitable for oral, buccal, nasal, topical, rectal or parenteral administration and may be prepared in a conventional manner using conventional excipients. For example for oral administration the pharmaceutical compositions may take the form of tablets or capsules. For nasal administration or administration by inhalation the compounds may be conveniently delivered as a powder or in solution. Topical administration may be as an ointment or cream and rectal administration may be as a suppository. For parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) the composition may take the form of, for example, a sterile solution, suspension or emulsion.

The dose of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, the route of administration, the form and severity of the condition and whether the compound is to be administered alone or in combination with another drug. Thus the precise dose will be determined by the administering physician but in general daily dosages may be in the range 0.001 to 100mg/kg preferably 0.01 to 50mg/kg.

BIOLOGICAL ACTIVITY

The following test was used to demonstrate the activity of compounds according to the invention:

Activity against tumour vasculature measured by fluorescent dye.

The following experiment further demonstrates the ability of the compounds to damage tumour vasculature.

Tumour functional vascular volume in CaNT tumour-bearing mice was measured using the fluorescent dye Hoechst 33342 according to the method of Smith *et al* (Brit J Cancer 57, 247-253, 1988). The fluorescent dye was dissolved in saline at 6.25 mg/ml and injected intravenously at 10 mg/kg 24 hours after drug treatment. One minute later, animals were killed and tumours excised and frozen; 10 μm sections were cut at 3 different levels and observed under UV illumination using an Olympus microscope equipped with epifluorescence. Blood vessels were identified by their fluorescent outlines and vascular volume was quantified using a point scoring system based on that described by Chalkley, (J Natl Cancer Inst, 4, 47-53, 1943). All estimates were based on counting a minimum of 100 fields from sections cut at the 3 different levels.

Induction of necrosis

Mice bearing either CaNT or SaS tumours were treated with the test compound and tumours excised after 24h, fixed in formalin, embedded in paraffin, sectioned and stained with haematoxylin and eosin. Sections were scored based on area of necrosis as follows:

% necrosis	score		% necrosis	score
0-10	1		51-60	6
11-20	2		61-70	7
21-30	3		71-80	8
31-40	4		81-90	9
41-50	5		91-100	10

Control tumours had mean scores of 2.0 (CaNT) and 1.0 (SaS). Mean values from at least three different tumours were obtained for each test compound.

Table: Reduction in Vascular Volume and Induction of Necrosis in the Carcinoma NT Tumour 24h Post Dose: Comparison with Combretastatin A4 phosphate (CA4P).

Compound	Dose	Vascular volume % reduction	Necrosis score
CA4P	50mg/kg i.v.	88	5.7
CA4P	50mg/kg i.p.	91	6.0
Cmpd. of Example 1	50mg/kg i.v.	98	10.0
Cmpd. of Example 2	50mg/kg i.p.	95	8.0

The following non-limiting Examples illustrate the invention:

EXAMPLE 1

(Z)-1-(4-Methoxy-3-N^G-nitroarginyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

Trifluoroacetic acid (0.2ml) was added to a solution of (Z)-1-(3-(N-α-t-butoxycarbonyl-N-ω-nitroarginyloxy)-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (82mg) in dichloromethane (3ml) at 0°C and the mixture allowed to come to room temperature and stir 16h. The mixture was concentrated under reduced pressure, ethanol (5ml) was added, the mixture was reconcentrated under reduced pressure and the procedure repeated three times. Trituration with diethyl ether afforded the title compound (69mg) as an off-white powder m.p. 157-159°C.

The (Z)-1-(3-(N-α-t-butoxycarbonyl-N-ω-nitroarginyloxy)-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene used in the above procedure was prepared as follows: A solution of (Z)-1-(3-hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (65mg, 0.21mmol), Nα-t-BOC-ω-nitro-L-arginine (134mg, 0.42mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (110mg, 0.54mmol) and 4-dimethylaminopyridine (5mg) in dichloromethane (2.1ml) was stirred at room temperature for 72h. The reaction mixture was partitioned between dichloromethane and water and the aqueous phase extracted with two portions of dichloromethane. The combined organic extracts were washed successively with two portions of water and one of brine, dried (MgSO4) and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with 33% ethyl acetate/hexane followed by 100% ethyl acetate to give (Z)-1-(3-(N-α-t-butoxycarbonyl-N-ω-nitroarginyloxy)-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (82mg) as a white oil.

EXAMPLE 2

(Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine methyl ester

A solution of (Z)-1-(3-hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (400mg, 1.27mmol) in dry pyridine (2ml) was added dropwise to a cooled (0°C) mixture of 4-nitrophenylchloroformate (282mg, 1.40mmol) and dry pyridine (1ml). After 20min the reaction mixture was warmed to room temperature and stirred for a further 6h. To this was added L-N^G-nitroarginine methyl ester hydrochloride (343mg, 1.27mmol, azeotroped with toluene) and the mixture heated (70°C) for 72h. After cooling to room temperature, the reaction mixture was partitioned (ethyl acetate, water), the organic layer was washed (water x3), the aqueous layer was extracted (ethyl acetate x3), the combined organic fractions were further washed (water x2, saturated $NaCl_{(aq)}$ x1), dried ($MgSO_4$), and concentrated *in vacuo*. Flash silica chromatography, eluting with 50% ethyl acetate/hexane then 100% ethyl acetate,

afforded the title compound as a white foam (292mg) . Elemental analysis: calculated C 54.26% H 5.78% N 12.17%, found C 53.97% H 6.07% N 11.55%.

EXAMPLE 3

(Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine

A mixture of (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine methyl ester (95mg, 0.165mmol), tetrahydrofuran (10ml), water (10ml) and concentrated sulphuric acid (1ml) were heated at 60°C for 72h. After cooling to room temperature, the reaction mixture was partitioned (ethyl acetate, water), the aqueous layer was extracted (ethyl acetate x3), the combined organic fractions were further washed (water x2, saturated $NaCl_{(aq)}$ x1), dried ($MgSO_4$), and concentrated in vacuo. The title compound was obtained as an opaque oil (90mg, 98%). LC-MS indicated purity >95%.

In a similar manner to Example 2 there was prepared:

EXAMPLE 4

(Z)-N-[2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine methyl ester

From (Z)-1-(3-hydroxy-4-methyl)-2-(3,4,5-trimethoxyphenyl)ethene (125mg, 0.42mmol), nitrophenylchloroformate (93mg, 0.46mmol) and L-N^G-nitroarginine methyl ester hydrochloride(113mg, 0.42mmol) there was obtained the title compound (15mg) as a colourless oil. LC-MS indicated purity >95%. MS (*m/z*) 300 (M^+), 285.

The (Z)-1-(3-hydroxy-4-methyl)-2-(3,4,5-trimethoxyphenyl)ethene used as starting material was prepared as follows:

A suspension of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide (8g, 15.3mmol) in tetrahydrofuran (450ml) at -23°C was treated with n-butyllithium (10ml of a solution in hexanes, 15.3 mmol) dropwise and the mixture stirred for 1h. 4-methoxy-

3-*tert*-butyldimethylsilyloxybenzaldehyde (4.07g, 15.3mmol) was added and the mixture stirred a further 4h at -23°C before warming to room temperature and stirring a further 16h. The mixture was poured on to ice-water (150ml) and extracted with diethyl ether (three portions of 150ml). The combined extracts were washed with water (three portions of 150ml) and brine (150ml), dried (MgSO4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexane followed by 15% ethyl acetate in hexane to give a white solid (4.61g) consisting of (Z)-1-(4-methyl-3-*tert*-butyldimethylsilyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene. A portion of this material (3.46g, 8mmol) was dissolved in tetrahydrofuran (60ml) and treated with tetrabutylammonium fluoride (8.3 ml of a 1.0M solution in tetrahydrofuran, 8.3mmol) and stirred for 20min. Ice (20g) was added and the mixture extracted with diethl ether (200ml). The extract was washed with water (three portions of 80ml), dried (MgSO4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with 40% ethyl acetate in hexane. 1-(3-hydroxy-4-methyl)-2-(3,4,5-trimethoxyphenyl)ethene (2.01g) was obtained as a white solid.

CLAIMS:

1. A vascular damaging agent which is a compound of formula IA

A-X-B

IA

Wherein

A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

2. A vascular damaging agent which is a compound of formula I

A-X-B

I

Wherein

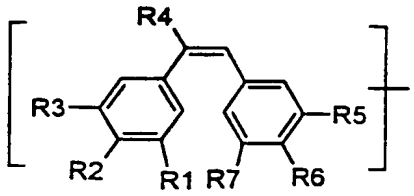
A is a substituted *cis*-stilbene moiety

X is a linker bond, atom or group

B is a moiety derived from an inhibitor of nitric oxide synthase

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

3. A vascular damaging agent according to claim 2 in which the *cis*-stilbene moiety is a group of formula II



II

Wherein

R1, R2 and R3 are each independently H, optionally substituted alkoxy, optionally substituted alkyl or halogen

R4 is hydrogen or cyano

R5, R6 and R7 are each independently H, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, halogen, amino, alkylamino, dialkylamino, cyano, nitro, carboxyl, alkanoyl, alkoxycarbonyl, alkoxycarbonyloxy, alkoxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylcarbonylamino, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, dialkylaminosulphonyl, alkylsulphonylamino, aminosulphonylamino, alkylaminosulphonylamino, dialkylaminosulphonylamino, mercapto, alkylsulphanyl or alkylsulphinyl,

with the proviso that at least two of R1, R2 and R3 must be optionally substituted alkoxy.

4. An agent according to either of claims 2 and 3 in which the linker group X is a bond.

5. An agent according to either of claims 2 and 3 in which the linker group is selected from an optionally substituted methylene chain, or $-(CH_2)_m-Y-(CH_2)_n-$ wherein Y is selected from -O-, -S-, -S(O)-, $-SO_2-$,-NH-, -Nalkyl-, -CO-, -OC(O)-, -

NHC(O)-, -N(alkyl)C(O)-, -NHC(O)NH-, -NalkylC(O)NH-, -NalkylC(O)Nalkyl-, -$NHSO_2$-, -NalkylSO_2-, -$NHSO_2NH$-, -NalkylSO_2NH-, -NalkylSO_2Nalkyl- and -OC(O)O-, m is 0-3 and n is 0-3.

6. An agent according to any one of claims 2 to 5 in which the nitric oxide synthase inhibitor moiety is selected from a group derived from an amino acid inhibitor of nitric oxide synthase. a thiocitrulline derivative, an S-alkylisothiourea derivative or 2-aminopyridine derivative.

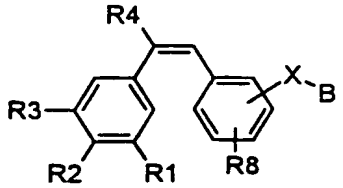
7. An agent according to claim 6 in which the group derived from an amino acid inhibitor of nitric oxide synthase is a group -C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio, or a group -NHCH(CO_2R10)-(CH_2)p-NHC(NH)Z where p and Z are as hereinbefore described and R10 is hydrogen or alkyl.

8. An agent according to claim 6 in which the thiocitrulline group is -C(O)CH(NH_2)-(CH_2)p-NHC(S)NH_2 or a group -NHCH(CO_2R10)-(CH_2)p-NHC(S)NH_2 .

9. An agent according to claim 6 in which the derivative of S-alkylisothiourea is -(CH_2)p-SC(NH)NH_2 .

10. An agent according to claim 6 in which the derivative of 2-aminopyridine is 4-methyl-2-pyridinylamino.

11. An agent according to claim 2 wherein the compound is



III

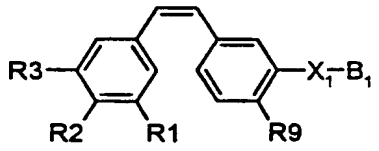
Wherein

R1, R2, R3, R4, X and B are as hereinbefore described

R8 is alkyl, amino, hydroxy, alkoxy or halogen

12. An agent according to claim 11 wherein the compounds are of formula III wherein R1, R2, R3, R4, are as hereinbefore described, R8 is alkyl, amino, hydroxy, alkoxy or halogen, X is -O- or -NH- and B is a group -C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio or a group -NHCH(CO_2R10)-(CH_2)p-NHC(NH)Z where p, Z and R10 are as hereinbefore described.

13. An agent according to claim 1 wherein the agent is of formula



IV

Wherein

R1, R2 and R3 are as hereinbefore described

R9 is alkyl, alkoxy or halogen

X_1 is O or NH

B_1 is a group -C(O)CH(NH_2)-(CH_2)p-NHC(NH)Z wherein p is 1-5 and Z is alkyl, alkylamino, dialkylamino, nitroamino, hydrazino or alkylthio.

14. An agent according to claim 2 which is selected from

(*Z*)-1-(4-Methoxy-3-N^G-nitroarginyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

(*Z*)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine methyl ester

(*Z*)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine

(Z)-N-[2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenoxycarbonyl]N^G-nitroarginine methyl ester

15. Use of a substituted stilbene compound in preparation of a medicament for the treatment of diseases involving neovascularisation characterised in that the stilbene compound is of formula IA

A-X-B

IA

Wherein

A is a substituted *cis*-stilbene moiety
X is a linker bond, atom or group
B is a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

16. Use of a substituted stilbene compound in preparation of a medicament for the treatment of diseases involving neovascularisation characterised in that the stilbene compound is of formula I

A-X-B

I

Wherein

A is a substituted *cis*-stilbene moiety
X is a linker bond, atom or group

B is a moiety derived from an inhibitor of nitric oxide synthase

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

17. A method for the treatment of diseases involving neovascularisation characterised by the administration of a stilbene derivative of formula I

A-X-B

IA

Wherein

A is a substituted *cis*-stilbene moiety
X is a linker bond, atom or group
B is a moiety derived from an inhibitor of the formation or action of nitric oxide in mammalian systems

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

18. A method for the treatment of diseases involving neovascularisation characterised by the administration of a stilbene derivative of formula I

A-X-B

I

Wherein

A is a substituted *cis*-stilbene moiety
X is a linker bond, atom or group
B is a moiety derived from an inhibitor of nitric oxide synthase

and the hydrates, pharmaceutically acceptable salts and prodrugs thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/00503

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61P35/00 A61P17/00 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 641 767 A (AJINOMOTO KK) 8 March 1995 (1995-03-08) abstract page 2, line 1 - line 40 examples tables 1,2 claims 1-10	1-18
X	WO 92 16486 A (ASTON MOLECULES LTD) 1 October 1992 (1992-10-01) abstract page 1, line 26 -page 3, line 25 page 3, line 27 - line 36 claims 1-18	1-18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 2000	25. 05. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Taylor, G.M.

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KOJI OHSUMI ET AL: "Novel Combretastatin Analogues Effective against Murine Solid Tumors: Design and Structure-Activity Relationships" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 41, no. 16, 30 July 1998 (1998-07-30), pages 3022-3032-3032, XP002102895 ISSN: 0022-2623 tables 1,2,4-6 Conclusion	1-18
X	OHSUMI K ET AL: "Syntheses and antitumor activity of cis-restricted combretastatins: 5-membered heterocyclic analogues" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 22, 17 November 1998 (1998-11-17), pages 3153-3158, XP004143718 ISSN: 0960-894X Introduction Compounds 4 and 5	1-18
X	GEORGE R PETTIT ET AL: "Antineoplastic Agents 322. Synthesis of Combretastin A-4 Produgs" ANTI-CANCER DRUG DESIGN,GB,BASINGSTOKE, vol. 10, no. 4, June 1995 (1995-06), pages 299-309-309, XP002102893 ISSN: 0266-9536 Summary Introduction Compounds 1e-1j, 2 page 306 -page 308	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/00503

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17 and 18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[illegible]onal Application No
PCT/GB 00/00503

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0641767 A	08-03-1995	AT 174899 T	15-01-1999
		CA 2131683 A	09-03-1995
		CN 1105967 A,B	02-08-1995
		DE 69415445 D	04-02-1999
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		ES 2126068 T	16-03-1999
		GR 3029603 T	30-06-1999
		JP 7228558 A	29-08-1995
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WO 9216486 A	01-10-1992	AU 1371992 A	21-10-1992